Fighting Drug Resistance in Russia: Challenges and Achievements

Wieslaw Jakubowiak, M.D.
WHO TB Control Programme in the Russian Federation

IOM Drug Forum Workshop: November 5, 2008
TB notification and mortality rates, TB-HIV level, Russian Federation

TB notification rate, per 100K
Mortality, per 100K
TB-HIV, % of all TB cases

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation

- TB notification and mortality rates, TB-HIV level, Russian Federation
### MDR-TB among new and all registered smear/culture positive pulmonary TB patients in Russia (National statistics), %

<table>
<thead>
<tr>
<th>Year</th>
<th>Among New Cases</th>
<th>Among All Cases</th>
<th>Number of MDR TB Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>6.7</td>
<td>18282</td>
<td>3173</td>
</tr>
<tr>
<td>2000</td>
<td>7.1</td>
<td>20519</td>
<td>3438</td>
</tr>
<tr>
<td>2001</td>
<td>8.9</td>
<td>20326</td>
<td>3500</td>
</tr>
<tr>
<td>2002</td>
<td>7.8</td>
<td></td>
<td>4167</td>
</tr>
<tr>
<td>2003</td>
<td>8.3</td>
<td></td>
<td>4056</td>
</tr>
<tr>
<td>2004</td>
<td>8.1</td>
<td></td>
<td>18.7</td>
</tr>
<tr>
<td>2005</td>
<td>9.5</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td>9.8</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td>21.4</td>
</tr>
</tbody>
</table>
MDR-TB among all pulmonary TB cases in the Russian regions, 2006
Extensively drug-resistant (XDR) TB among new and previously treated cases in Vladimir and Orel Oblasts, Russia (WHO pilot sites)

(Cross-sectional survey 01/01-31/12/2006)

<table>
<thead>
<tr>
<th>Oblast</th>
<th>MDR-TB strains tested to SLD</th>
<th>XDR-TB among new cases</th>
<th>XDR-TB among retreatment cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vladimir</td>
<td>182</td>
<td>0</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Orel</td>
<td>75</td>
<td>1 (6%)</td>
<td>15 (26%)</td>
</tr>
</tbody>
</table>
### Chronology of GLC-approved Projects/ 4th round GF-supported

<table>
<thead>
<tr>
<th>Year</th>
<th>No. projects approved by GLC</th>
<th>No. MDR-TB patients could be enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1 projects</td>
<td>790</td>
</tr>
<tr>
<td>2006</td>
<td>4 projects</td>
<td>1 400</td>
</tr>
<tr>
<td>2007</td>
<td>14 projects</td>
<td>3 800</td>
</tr>
<tr>
<td>2008</td>
<td>24 projects</td>
<td>6 546</td>
</tr>
<tr>
<td>2009</td>
<td><em>(planned)</em> 28 projects</td>
<td>7 500</td>
</tr>
</tbody>
</table>

Additionally, Tomsk project has been active since 2000
Schedule of MDR-TB patient enrollment onto treatment, 4th round GF project

(Excludes Tomsk Oblast)
Capacity building for DOTS-Plus expansion (1)

- Develop national guidelines on treatment of MDR-TB patients based on international recommendations

- Strengthen capacity of the laboratory network, including:
  - Training modules on culture/DST and microscopy have been developed and approved by the MoHSD
  - Equipment has been provided for microscopy centers and bacteriological laboratories in civilian and prison sectors; laboratory renovations (WB and GF projects)
  - Proficiency testing of laboratory drug susceptibility testing: 3 rounds of DST PT were conducted with supranational reference laboratory from 2005-2007. Expanded national PT (~150 labs) supported by GF in 2007 and 2008.

- Expand Drug Resistance Survey (DRS) activities to get a better understanding of the epidemiological situation nationwide

- Implement new recording and recording system on MDR-TB
Capacity building for DOTS-Plus expansion (2)

- Build adequate in-patient capacities for treatment of MDR-TB cases (GF project: establish 13 centers of excellence in the civilian and prison sectors)

- Strengthen human resources:
  - In 2005-2008, the Federal TB Research Institutes, Federal Correctional Service in cooperation with Partners in Health and WHO provided 6 workshops on MDR-TB for staff of TB Research Institutes, regional TB services and TB services of prison sector (380 participants); and 23 trainings for lab staff (365 participants)
  - In 2007-2008, the GLC/WHO provided 5 trainings on MDR-TB management (72 participants). In 2007, a Demonstration Center on MDR-TB management was established in one of the regions.

- Implement infection control standards and provide equipment and renovations for TB treatment facilities and laboratories in civilian and penitentiary sectors (GF project). Establishment of 2 Demonstration Centers in infection control.
Drug supply through the GLC mechanism

Achievements:

In 2007-2008, SLD for enrollment of 1,500 MDR TB patients were supplied.

RHCF has paid IDA for provision of SLD for enrollment of new 1,500 MDR TB patients (2 shipments are expected in November–December 2008 and February 2009).

Challenges:

There is not a reliable system for SLD provision through the GDF/IDA mechanism.

There is not correspondence between IDA rules and national regulations.
A manufacturer presents documents and information for expertise

Specific Center for Medical Drugs expertise

Institute for standardization of medical drugs

Institute for preclinical and clinical expertise of medical drugs

Pharmacological expertise

Special commissions of Specific Center for Medical Drugs expertise

Federal Service for Health and Social Development

Certificate
PROCESS OF DRUG CERTIFICATION AT THE FEDERAL SERVICE FOR HEALTH AND SOCIAL DEVELOPMENT IN THE RUSSIAN FEDERATION

Applicant

Set of documents

Receipt of documents for expert examination

Management Department

Law Department
(identification of rights)

Unification Department
(review of drug title, manufacturer, country)

Drugs samples

Department of document circulation
(sending documents to examination bodies)

The Institute for the State Control of Drugs or Department of Approbation of the Institute for Standardization of Drugs (quality and reproducibility of methodology assessment)

Analysis protocol

The Institute of Pre-clinical and Clinical Expertise of Drugs (examination of effectiveness and safety data)

Instruction on use

The Institute for Standardization of Drugs (examination of draft regulations, drugs quality requirements)

Regulations

Data on clinical and pre-clinical testing

Federal Service for Health Care and Social Development (approval of regulations, instruction, signing Registration certificate)

Handover of the file with examination outcomes for making decision on state registration

Final examination

Department of examination and information (data verification, unification)

Management Department (final unification control)
Constraints in Drug Management

- Long drug registration process: up to one year, with fast-track registration of 6 - 7 months
- Drug quality monitoring during commercial distribution
- Unclear procedure of SLD needs assessment: absence of national guidelines, lack of training materials and experts
- Drug management at federal and regional levels: unclear distribution of responsibilities
- Drug management at regional level: lack of trained staff, problems in distribution
- Difficulties with import procedures of SLD drugs via GDF/IDA in framework of the 4th round GF project
Average cost of anti-TB drugs
GDF/IDA vs local market, 2003-2008
USD per mg
### Number of SLD manufacturers in the Russian market

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total manufacturers</th>
<th>Domestic manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cm</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Cs</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Eto</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Km</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ofx</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>PAS</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>
GMP and Pre-qualification

- 8 Russian pharmaceutical manufacturers participated in 3 trainings in 2006 organized by WHO HQ/EURO/Russia.
- 5 Russian manufacturers confirmed EU GMP compliance in 2006-07 as a result of international inspections (WHO CC “Pharmacon”, Denmark inspections in framework of WHO GF/RHCF project):
  - Zio-Zdorovie
  - Makiz-Farma
  - Pharmstandard-Lekarstva
  - Veropharm
  - Scopin-Pharm
- Three of them expressed their willingness to participate in the WHO/HQ pre-qualification, but still no one applied - Low rate and very slow involvement into pre-qualification
- Low motivation for manufacturers to be a part of pre-qualification process, as well as selling drugs at concessional prices
- Due to high staff turnover in the Russian pharmaceutical industry, information about pre-qualification should be repeatedly spread among manufacturers.
SLD procurement for the 4th round GF project in Russia

Dec 1, 2005

4th round GF project initiation

Dec 1, 2006

Signing of contract 1 (August 2006)

Lack of drug registration

Dec 1, 2007

End of Phase
One of the GF Project

Customs clearance of drugs in contract 1 (August 2007)

Only 200 patients on treatment

Drugs arrive at customs contract 1 (May 2007)

Problems with import documentation

Contract alterations

Signing of contract 2 (May 2007)

Global shortages of drugs
SLD procurement for the 4th round GF project in Russia

- **Dec 1, 2007**: Start of Phase Two of 4th round GF project
- **Delivery of drugs under contract 2 (May-September 2008)**
- **Contract 3 signed (May 2008)**
- **Delivery of drugs under contract 3 (August 2008)**
- **1,500 patients expected to be on treatment (Dec 31, 2008)**
- **6,000 patients expected to be on treatment**

**Established GF indicator:**

- **Dec 1, 2008**: 3,500 patients on treatment
Conclusions

Increasing financial support from government and international partners during recent years has allowed for improvements and upgrades to the TB control system.

The growing number of MDR/XDR-TB cases in Russia calls for urgent expansion of internationally accepted standards for MDR management.

Continuation of the 4th round GF project is important to accelerate expansion of MDR management.

A reliable mechanism to ensure provision of WHO pre-qualified second line drugs should be urgently addressed.

The WHO pre-qualification process should continue to be promoted among local manufacturers in order to strengthen the local capacity in provision of drugs of proven quality. Pre-qualification training for Russian manufacturers should be continued.